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THE INDUSTRIAL INJURIES ADVISORY COUNCIL

POSITION PAPER 25

The association between shift working and (i) breast cancer (ii) ischaemic heart disease

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The association between shift working and (i) breast cancer, (ii) ischaemic heart disease

Position paper 25

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Summary

1. In 2008 the Danish National Board for Industrial Injuries elected to offer compensation to women who developed breast cancer following a long history of shift working. In view of the potential importance of the topic, the Industrial Injuries Advisory Council (IIAC), which advises the Secretary of State on matters relating to the Industrial Injuries Scheme, decided to consider the case for prescription. In addition, since the possible association between shift working and ischaemic heart disease (IHD) has also been the subject of a recent Danish review and of major research interest, the Council decided to consider, concurrently, the evidence relating to this question. This position paper summarises IIAC's consideration of the evidence on both subjects and records its conclusions.

2. The requirements for prescription differ between the UK and Denmark, notably in respect of the need in the UK to demonstrate, not only a causal link between an agent and a disease, but also a doubling of risk in those exposed to the agent in question, at least under some well-defined circumstances of exposure. Thus, in accordance with the legal requirements for prescription, the Council has sought robust epidemiological evidence that the risk of disease (breast cancer or IHD) is more than doubled in relation to shift work.

3. In respect of shift working and breast cancer, the Council reviewed the research report submitted to the Danish National Board, and the evidence considered by the International Agency for Research on Cancer (IARC) in its recent monograph on the carcinogenicity of shift working (IARC, 2007), the conclusions of which influenced the Danish government's decision.

4. The Council also considered the findings of two further reports: a review commissioned by the Health and Safety Executive (HSE) (Swerdlow, 2003), and the report of an expert meeting convened by the Institute for Environment and Health (IEH), University of Leicester (IEH, 2005). Finally, IIAC conducted its own literature search to ensure that no further studies of note had been published since the publication of these reports.

5. Of several studies considered, the majority showed a slightly increased risk of breast cancer associated with shift working. The dataset included two large, well-conducted cohort studies, a morbidity study and two case control studies. In the case of the cohort studies this increased risk was associated with more than 20 years of night work. One case control study reported no increased risk. The results of a meta-analysis of 13 studies similarly supported a moderately increased risk. However, in only two relatively small case control studies was a doubling of risk identified. The review commissioned by the Danish National Board described the human evidence for a causal association between nightshift work and breast cancer as 'limited' and the results as "sensitive to bias, chance and confounding".

6. In respect of shift working and IHD the Council considered the findings of a recent comprehensive review of the evidence (Frost *et al.,* 2009), commissioned by the Danish Working Environment Foundation, and an earlier systematic review on the topic (Bøggild and Knutsson, 1999), and carried out its own literature search to ensure that no recently published studies of note had been omitted from the dataset.

7. The Frost review drew attention to certain methodological limitations in the field of inquiry, notably the variation in definition of shift work and the failure to make adjustments in the analysis for potential confounders. Notwithstanding these limitations, the 11 studies which reported relative risks were consistent

in identifying moderately increased risks of IHD in shift workers. In the majority of these studies relative risks were below 2.0. Only one study reported a relative risk which was more than doubled, whilst a further study reported a more than doubling of risk in those with more than 11 years of shift working, although this was not repeated in those whose shift working exceeded 21 years. Frost *et al.* reported that "in a majority of the studies, we could not reasonably rule out negative or positive bias', due the quality of exposure information or confounder control."

8. The Council's further review confirmed that risks of IHD, if present, are only mildly elevated, with potential for certain non-occupational factors to confound relationships.

9. The Council has concluded that the case for prescription is insufficiently established for either condition. However, the Council undertakes to keep the evidence in respect of both these diseases under review and, in particular, to take note of the findings of an ongoing study of shift working and breast cancer, commissioned by the HSE, which is due to report in 2011.

This report contains some technical terms, the meanings of which are explained in a concluding glossary.

Background

10. IIAC is an independent statutory body that advises the Secretary of State for Work and Pensions in Great Britain and the Department for Social Development in Northern Ireland on matters relating to the IIDB scheme. This scheme provides a benefit that can be paid to an employed earner because of an industrial accident or prescribed disease. The major part of the Council's time is spent considering whether the list of prescribed diseases for which benefit is paid should be enlarged or amended.

11. In March 2009, the attention of the Council was drawn to a decision by the Danish National Board for Industrial Injuries to provide compensation to women who developed breast cancer following long experience (typically more than 20 years) of night shift work. Given the potential importance of this topic, IIAC elected to review the relation between shift work and breast cancer. In addition, the Council noted that there was a substantial and growing body of evidence relating to the possible association between shift working and IHD, which had also been the subject of a recent Danish review. The Council, therefore, decided to review the case for prescription in relation to shift working and each disease. This position paper summarises the Council's considerations, its further investigations and its conclusions.

Introduction

12. The decision of the Danish Government to compensate women who developed breast cancer following a history of night working was based largely on the conclusions of the World Health Organisation's International Agency for Research on Cancer (IARC), which carried out an expert review of the data in 2007 (IARC, 2008).

13. IARC's expert working group considered the findings of eight epidemiological studies and concluded that six of these studies provided evidence of a moderately increased risk in breast cancer in those who had carried out shift working for many years. However, IARC drew attention to certain limitations in the data, notably the possible influence of other factors on the results, the inconsistency across studies in the definition of shift work and the fact that the studies focussed largely on specific occupations, notably nurses and flight attendants.

14. IARC also considered the results of several rodent studies which investigated the effect of reducing the normal night-time production of the hormone melatonin by removal of the pineal gland in the brain (where melatonin is produced). The depression of melatonin has been suggested as a possible mechanism which is implicated in the development of tumours following disruption of the circadian system. Some of these studies indicated an increase in tumours, or in the rate of growth of tumours, in animals so treated.

15. IARC operates within a classificatory framework in which agents are graded in terms of their potential carcinogenicity, taking into account both human and animal data. Thus agents are graded on a scale as follows: Grade 1 (carcinogenic to humans), Grade 2a (probably carcinogenic to humans), Grade 2b (possibly carcinogenic to humans), Grade 3 (not classifiable from the evidence) and Grade 4 (probably not carcinogenic to humans). On the basis of their review of the human and animal studies referred to above, and taking account of the methodological limitations observed, shift work was graded as 2a, there being good animal data and limited human data on risks of the disease. The Danish National Board considered that, within the terms of the Danish system of compensation, a grade 2a classification constituted sufficient grounds for prescription.

16. It should be noted, however, that the requirements for prescription within the Danish system of compensation differ somewhat from those of IIAC[1]. In particular, within the Danish system, the focus is on the demonstration of a possible causal link, with less account taken of the magnitude of the effect. By contrast, within the UK system, there are specific legal requirements associated with prescription which have a bearing on the magnitude of disease risk that must be present. These requirements are described below.

[1] An International Comparison of Occupational Disease and Injury Compensation Schemes. www.iiac.org.uk

The legal requirements for prescription

17. The Social Security Contributions and Benefits Act 1992 states that the Secretary of State may prescribe a disease where he is satisfied that the disease:

    i. ought to be treated, having regard to its causes and incidence and any other relevant considerations, as a risk of the occupation and not as a risk common to all persons; and

    ii. is such that, in the absence of special circumstances, the attribution of particular cases to the nature of the employment can be established or presumed with reasonable certainty.

18. In other words, a disease may only be prescribed if there is a recognised risk to workers in an occupation, and the link between disease and occupation can be established or reasonably presumed in individual cases.

19. In seeking to address the question of prescription for any particular condition, the Council first looks for a workable definition of the disease. It then searches for a practical way to demonstrate in the individual case that the disease can be attributed to occupational exposure with reasonable confidence. For this purpose, reasonable confidence is interpreted as being

based on the balance of probabilities according to available scientific evidence.

20. Within the legal requirements of prescription it may be possible to ascribe a disease to a particular occupational exposure in two ways – from specific clinical features of the disease or from epidemiological evidence that the risk of disease is at least doubled by the relevant occupational exposure.

Clinical features

21. For some diseases attribution to occupation may be possible from specific clinical features of the individual case. For example, the proof that an individual's dermatitis is caused by his/her occupation may lie in its improvement when s/he is on holiday and regression when s/he returns to work, and in the demonstration that s/he is allergic to a specific substance with which s/he comes into contact only at work. It can be that the disease *only* occurs as a result of an occupational hazard (e.g. coal workers' pneumoconiosis).

Doubling of risk

22. Other diseases are not uniquely occupational, and when caused by occupation, are indistinguishable from the same disease occurring in someone who has not been exposed to a hazard at work. In these circumstances, attribution to occupation on the balance of probabilities

depends on epidemiological evidence that work in the prescribed job, or with the prescribed occupational exposure, increases the risk of developing the disease by a factor of two or more.

23. The requirement for, at least a doubling of risk is not arbitrary. It follows from the fact that if a hazardous exposure doubles risk, for every 50 cases that would normally occur in an unexposed population, an additional 50 would be expected if the population were exposed to the hazard. Thus, out of every 100 cases that occurred in an exposed population, 50 would do so only as a consequence of their exposure while the other 50 would have been expected to develop the disease, even in the absence of the exposure. Therefore, for any individual case occurring in the exposed population, there would be a 50% chance that the disease resulted from exposure to the hazard, and a 50% chance that it would have occurred even without the exposure. Below the threshold of a doubling of risk only a minority of cases in an exposed population would be caused by the hazard and individual cases therefore could not be attributed to exposure on the balance of probabilities; above it, they may be.

24. The epidemiological evidence required should ideally be drawn from several independent studies, and be sufficiently robust that further research at a later date would be unlikely to overturn it.

The diseases of inquiry

25. **Breast cancer** is common malignancy, which carries a lifetime risk of 1 in 9 among women. More than 45,000 women in the UK are diagnosed with the disease each year. Worldwide, breast cancer is the second most common type of cancer and the fifth most common cause of cancer death. Survival rates have improved markedly in recent decades with the advent of drug treatment to complement or replace surgery.

26. A number of established non-occupational factors have an important influence on risk of breast cancer. In particular, epidemiological evidence indicates that early menarche (early onset of menstruation), delayed menarche (later menopause), nulliparity (never having been pregnant) or having fewer pregnancies, and later age at first pregnancy, are risk factors for the disease. Oestrogen-containing hormone replacement therapy may confer risks in later life, as may being overweight and consuming more alcohol. Many of these factors share in common a capacity to increase total exposure to oestrogens, which in turn may influence the rate at which breast tissue cells divide and the chance of spawning pre-cancerous cells.

27. **Ischaemic heart disease** (disease involving the heart or blood vessels) (IHD) arises when the arteries that supply the heart and body with oxygen and nutrients become narrowed by atherosclerosis, a condition in which an artery wall thickens as a result of the build-up of fatty materials. This restricts the supply of blood and oxygen, particularly during exertion. A ‘heart attack’ (myocardial infarction (MI)) occurs when the blood supply to a part of the

heart muscle is completely interrupted, usually because a blood clot forms in a diseased coronary artery that is already narrowed by atherosclerosis. IHD is the leading cause of death in Britain, the US, and most European countries.

28. Well-established non-occupational risk factors for the disease include: smoking, high blood pressure, diabetes, high levels of blood fats, black or Asian ethnic background, increasing age, gender and family history (e.g. of high cholesterol, high blood pressure, or early MI).

29. Shift workers and non-shift workers may differ in terms of their non-occupational risk factors for breast cancer and IHD. For example, opportunity to undertake shift work may be greater in women who do not have children at home; while shift workers may differ from their colleagues in other characteristics, such as smoking habits, diet, weight, alcohol intake, and uptake of preventive medical services. Thus, ideally, studies of shift working and breast cancer or ischaemic heart disease would consider, and allow for, a range of potentially confounding reproductive and demographic characteristics. Later studies in each domain of inquiry have been more successful in this respect than earlier investigations.

Summary of the evidence

30. Since neither breast cancer nor IHD has unique clinical features when found in an occupational setting, the case for prescription in each disease rests on the availability of epidemiological evidence which demonstrates a doubling of

risk in shift workers when compared to other workers. Also, as both conditions are multifactorial, thus there is a need to demonstrate an increased risk when other potential confounders have been taken into account (paragraph 29).

Shift working and breast cancer

31. IIAC has based its considerations on four recent comprehensive reviews, that of IARC (2007) noted above, the review commissioned by the Danish National Board to inform its decision, and two earlier reviews - the report of an expert meeting convened by the IEH, University of Leicester (IEH, 2005) and a report commissioned by the HSE (Swerdlow, 2003). These reports cover a number of key studies in different countries and among different occupations, summarized briefly below. In addition, the Council performed a literature review of its own to ensure that more recent research reports of note were also considered.

32. Hansen (2001) conducted a record linkage case control study in Denmark. Individual employment histories, dating from 1964, were derived from a nationwide pension scheme with compulsory membership. This was linked to information from the Danish Cancer Registry which identified 7035 women with breast cancer at ages 30-54 and born between 1935 and 1959. Occupations involving night work were classified by reference to information from a national survey of the occupations of 2603 women in one year (1976). The odds ratio (OR) for breast cancer in women who had worked for at least six months in one of the occupations thus classified, compared to age-

matched controls was 1.5 (95% confidence interval (CI) 1.2 to 1.7). Although in this study adjustment was made for socio-economic status and mother's age at birth of first and last child, no account was taken of other potential confounders, notably alcohol consumption and other reproductive factors.

33. A case control study in the US (Davis *et al.*, 2001) involved 813 cases of breast cancer identified from a population-based cancer registry, aged 20 to 74 years, and 793 age-matched controls. Women were personally interviewed to obtain information about their occupational histories. The OR for ever having worked for at least six months on what was termed the 'graveyard shift' (defined as eight hours between 7 pm and 9am) was 1.6 (95% CI 1.0 to 2.5). Control for potential confounders was very limited in this study. In particular, there was no adjustment for socioeconomic status, alcohol consumption, age of first pregnancy, age of menarche or menopausal status.

34. By contrast O'Leary *et al.* (2006) in the US compared 576 breast cancer cases with 585 population-based controls and found that night shift workers were at lower risk than women who had never worked shifts (OR 0.55, 95% CI 0.32-0.94). There was also no significantly increased risk for shift workers overall (OR 1.04, 95% CI 0.79-1.38) or for evening shift workers (OR 1.08, 95% CI 0.81-1.44). In this study a range of potential confounders were included in the analysis, namely alcohol consumption, education, household income, race, parity, experience of breastfeeding, mammography, history of benign breast disease, family history of breast cancer, use of oral contraceptives and hormone replacement therapy.

35. Schernhammer *et al.* (2001) followed 78,562 women who were part of the wider US study of Nurses' Health. Follow-up was over 10 years. Adjustment was made for a range of potential confounding variables which included parity, age at first birth, body mass index, alcohol consumption, oral contraception use, post menopausal hormone use and menopausal status. There was a moderately increased risk of breast cancer in women who worked on rotating night shifts for 1-14 years (Relative Risk (RR) 1.08, 95% CI 0.99-1.18) and for 15-29 years (RR 1.08, 95% CI 0.90 – 1.30). For women who worked more than 30 years on these shifts the RR was 1.36 (95% CI 1.04-1.78).

36. A further study by Schernhammer *et al.* (2006) was restricted to premenopausal women. A cohort of 115,022 was followed for a 12 year period from 1989. Women who reported more than 20 years of rotating night shift work showed an elevated risk of breast cancer (RR 1.79, 95% CI 1.06-3.01) compared to those who did not report such work.

37. Schwartzbaum *et al.* (2007) carried out a morbidity study in Sweden involving a cohort of 2,102,126 men and 1,148,661 women derived from 1960 and 1970 Swedish census data which identified workers employed on shift work for at least 20 hours per week in both years. These were followed up from 1971 to 1989 in terms of a range of cancer sites. The Standard Incidence Ratio (SIR) for breast cancer in female shift workers compared with non-shiftworkers was 0.94 (95% CI 0.74-1.18).

38. The aforementioned studies indicated either a near absence of increased risk or a risk which falls short of the ‘doubling of risk’ threshold that IIAC normally applies in recommending prescription. However, two studies reported an increased risk which was more than doubled. Tynes *et al.* (1996) carried out a nested case control study involving 50 cases of breast cancer occurring in a cohort of 2619 female radio and telegraph officers working in merchant shipping who were initially studied in relation to possible effects of radiation exposure. Cases were matched to between four and seven controls from the original cohort and classification of shift working was carried out on the basis of work records. There was no association between the risk of breast cancer and shift work at ages below 50 years but a significant association in those aged 50 and above. Classification into categories of exposure to shift work showed a marked increased risk in those in the highest category versus those with no experience of shiftwork (RR 6.1 95%, CI 1.5 to 24.2). However, the basis of the definition and categorization of shift work was unclear. This was a relatively small study and CIs were wide. Moreover, with the exception of information on parity and age of first pregnancy on a small number of subjects, there was no information available to the researchers on potential confounders.

39. Lie *et al.* (2006) carried out a nested case control study among a cohort of 44,835 Norwegian nurses. Here four controls were individually matched by year of birth to each of 537 breast cancer cases, occurring between 1960 and 1982. Work histories were constructed from information on the nurse registry

and data from census records. The OR for breast cancer in nurses who had worked nights for 30 years or more compared with those who had not worked nights following graduation was 2.21 (95% CI 1.10-4.45). However, there was little account taken of potential confounders in this study. Adjustment was made only for parity and duration of employment.

40. The conclusions of a systematic review and meta-analysis of 13 studies, which included six of those described above excluding O'Leary and Schartwbaum *et al.,* (Megdal *et al.* (2005) supported a moderately elevated risk in those with a long history of night work – the overall estimated risk for all studies combined being 1.48 (95% CI 1.36-1.61). However, the authors noted the difficulty of adjusting for potential confounders in this field and the tendency of investigators to study a narrow range of occupations.

41. The review commissioned by the Danish National Board described the human evidence for a causal association between nightshift work and breast cancer as 'limited', and the results as "sensitive to bias, chance and confounding".

Summary and conclusions on shift working and breast cancer

42. Taken together the data suggest the possibility of a moderately elevated risk of breast cancer associated with prolonged (more than 20 years) night work. However, the evidence base is limited by the methodological difficulties identified in the IARC monograph, associated with inconsistency in the definition of shift work and incomplete adjustment for other important non-

occupational risk factors. Importantly, in the context of the requirements of IIAC, the results of most studies fail to meet the threshold of a doubling of risk. IIAC is, therefore, unable to recommend prescription on the basis of currently available evidence. However, the Council undertakes to keep the position under review and, in particular, to take note of the findings of an ongoing study of shift working and breast cancer, commissioned by the HSE, which is due to report in 2011.

Shift working and IHD

43. IIAC has based its consideration of the evidence primarily on the recent systematic review carried out by Frost *et al.* (2009) on behalf of the Danish Working Environment Foundation; but also on an earlier systematic review by Bøggild and Knutsson (1999), (consistent with Frost's observations), and a targeted literature review by the Council's Research Working Group.

44. Frost *et al.* considered the results of 16 studies which investigated the association between ischaemic heart disease (IHD)[2] and shift working. Of these, two studies had inadequately defined outcome measures and two did not report relative risks. The results of the remaining 12 studies are summarised briefly below.

[2] Frost *et al.*. note that IHD includes angina, MI and acute and chronic ischemic heart disease, in accordance with the International Classification of Diseases.

45. Five case control studies are included in the dataset. Of these, three included only fatal cases. McNamee *et al.* (1996) carried out a nested case control study involving 467 cases (deaths from IHD before the age of 76) among male manual workers at a UK company. Information on shift work was obtained from company records. Compared to controls from the same company, matched for age and year of hire, the OR for shift working versus day work (adjusted for other risk factors such as height, weight and blood pressure) was 0.85 (90% CI 0.65-1.12). However, no information on work patterns before or after working at the company was collected.

46. A further nested case control study, using similar methods, was carried out on a different industrial cohort (workers employed at a nuclear fuel company in the UK) by Yedergarfer and McNamee (2008). There were 635 cases (deaths due to IHD before the age of 75) and an equal number of controls matched for age, year of hire and work status. The OR for death from IHD in shift workers, adjusted for social class was 1.03 (90% CI 0.83-1.28). Again no information on work patterns before or after working at the company was collected.

47. Steenland and Fine (1996) also carried out a nested case control study involving 163 cases (deaths from IHD) among a cohort of 21,491 male workers at four plants in the US. Each case was matched to five controls in terms of age, race, plant and work status. The OR for evening workers versus

day workers was 1.01 (95% CI 0.66-1.52) and for night shift workers versus day shift workers was 0.64 (95% CI 0.28-1.47).

48. Two case control studies included both fatal and non-fatal cases. Alfredson *et al.* (1982) carried out a case control study in Sweden involving 334 cases with fatal or non-fatal MI from two Swedish hospitals between 1974 and 1976. They were compared with 882 age-matched controls. Shift working, based on interview data, was classified as at least 50% of work involving alternating day and night working. Age-adjusted RR for MI in shift workers was 1.25 (95% CI 0.97-1.62).

49. Knutsson *et al.* (1999) also carried out a population-based case control study in Sweden involving 2006 cases of MI (fatal and non-fatal) from two geographical regions of Sweden. These were matched to 2642 controls in terms of age, gender and geographical region. Shift work was assessed by questionnaire in terms of the last five years of work. Those who reported working between the hours of 18.00 and 06.00 were categorised as shift workers. The RR for MI in shift workers, adjusted for job strain, educational level and smoking, was 1.3 (95% CI 0.9-1.8) in males and 1.6 (95% CI 0.8-3.1) in females.

50. Knutsson *et al.* (1986) followed up a cohort of 504 workers in the Swedish paper industry employed on three shift rotas involving day, evening and night

work. They reported a relative risk of 1.4 overall for self-reported IHD, including both angina and MI, (some of which was checked by health records) which was non-significant. Analysis by years of shift work showed RRs of 1.5 for 2-5 years (non-significant) 2.0 for 6-10 years (non-significant), 2.2 for 11-15 years (p=0.04), 2.8 for 16-20 years (p=0.03), and 0.4 for 21+ years (non-significant).

51. Tüchsen (1993) carried out a four-year follow-up of Danish men, identified in central registers, aged 20-59 in January 1981. Occupational grouping was allocated on the basis of existing occupational survey data. Data on first time hospitalisation for IHD was used to calculate standardised hospitalisation ratios (SHRs) for different occupational groups based on their pattern of working hours. For those working predominantly at night and early morning the SHR was 1.93 (90% CI 1.583- 2.36). For work covering 24 hour services this was 1.68 (90% CI 1.518-1.86). No control for important confounders such as socioeconomic status and smoking was included.

52. Tenkanen *et al.* (1997) carried out a seven-year follow up of 1086 males employed in five industrial companies in Finland. Data were collected on a range of physical and psychosocial risk factors. The adjusted risk ratio for shift workers versus day workers was 1.38 (95% CI 1.01-1.89).

53. Bøggild *et al.* (1999) carried out a 22-year follow-up of 5249 male Danish workers recruited from a range of industries. Workers who did not work solely within daytime hours were classified as shift workers. This study also collected information on other physical and psychosocial risk factors and reported an adjusted RR for fatal and non-fatal incidents of IHD of 0.9 (95% CI 0.7-1.1) among shift workers.

54. Kawachi *et al.* (1995) carried out a four-year follow-up of 79,109 female nurses who in 1988 had completed a questionnaire about shift working patterns and other risk factors. In 1992 cases of non-fatal MI (number = 248) were identified by self-report and fatal cases (number = 44) were traced from death registers. The adjusted RR for shift working was 1.31 (95% CI 1.02-1.68). This increased to 1.60 (95% CI 1.05-2.42) with six years of shift working but did not increase further with longer duration.

55. Karlsson *et al.* (2005) conducted a follow-up of 2354 shift workers and 3088 day workers employed in two Swedish pulp and paper plants for at least six months between January 1940 and December 1998 who were less than 60 years of age at first employment. Duration of shift work was assessed from company records. Deaths from IHD were identified from national death registers. The overall age-adjusted RR for shift working was 1.11 (95% CI 0.95-1.30). Analysis by duration of exposure showed the highest RR to be in those with more than 30 years of shift work (RR 1.24, 95% CI 1.04-1.49).

56. Fujino *et al.* (2006) followed 17,649 Japanese males, in full-time employment between 1988 and 1990, until 2003. Information about shift work and a range of physical and psychosocial risk factors was obtained by questionnaire. The adjusted RR for all shift workers, based on 86 deaths from IHD, was 2.32 (95% CI 1.37-3.95). For night workers this was 1.23 (95% CI 0.49-3.10).

Summary and conclusions on shift working and IHD

57. The authors of the review by Frost *et al.* concluded that there was limited evidence of a causal association between shift work and IHD, although they drew attention to a number of methodological difficulties in the data summarised above. In particular they noted the variable definition of shift work and, in the case of several studies, the failure in design and analysis to allow for other non-occupational risk factors that might explain the observed associations (e.g. higher prevalence of smoking, hypertension, diabetes in the shift workers). Frost *et al.* commented that "in a majority of the studies, we could not reasonably rule out negative or positive bias', due the quality of exposure information or confounder control."

58. The findings by Frost *et al.* mirror those of a systematic review one decade earlier, by Boggild and Knutsson (1999). On that occasion a review of 17 studies suggested on balance that risks of IHD were increased 40% in shift workers (RR about 1.4). But in most studies methodological problems

("related to selection bias, exposure classification, outcome classification and the appropriateness of comparison groups") were apparent.

59. Notwithstanding the limitations identified, a substantial body of studies in different countries using different methodologies suggest with a high level of consistency that risks of IHD in shift workers are increased only slightly, if at all . Only one study (Fujino *et al*., 2006) reported a relative risk which was more than doubled in shift workers overall (although not in night workers). In addition, one study (Knutsson *et al..,* 1986) identified a doubling of risk in workers who had worked on shifts for more than 11 years, although this trend was inconsistent in that the risk was small and statistically insignificant in those with a longer duration of shift work (more than 21 years).

60. In conclusion, the results of the majority of studies fail to meet the required threshold of a doubling of risk; and IIAC is therefore unable to recommend prescription of IHD in shift workers.

Prevention

61. HSE does not presently regard the evidence about shift work and cancer as such that employers should be asked to do more to protect the health of their shift workers than is already required by the Working Time Regulations 1998 and HSG 256.

62. The principal established risk from shift work is fatigue, which can contribute to human error, accidents and injuries. To help employers comply with their legal duties, HSE has produced guidance on assessing and managing the health and safety risks of shift work and fatigue. **Managing shift work: Health and Safety Guidance HSG 256** includes background information on the health and safety risks associated with shift work and fatigue, UK legal duties and practical guidance on how to reduce the risks. A short summary of the guidance, including the good practice guidelines, is available on the HSE website at http://www.hse.gov.uk/humanfactors/shiftwork/index.htm .

Diversity and equality

63. The Industrial Injuries Advisory Council is aware of issues of equality and diversity and seeks to promote as part of its values. The Council has resolved to seek to avoid unjustified discrimination on equality grounds, including age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, gender and sexual orientation. During the course of the review of shift work and breast cancer or ischaemic heart disease, no diversity and equality issues became apparent.

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Appendix: A glossary of terms used in this report

Types of study

Case-control study: A study which compares people who have a given disease (cases) with people who do not (controls) in terms of exposure to one or more risk factors of interest. Have cases been exposed more than non-cases? The outcome is expressed as an **Odds Ratio**, a form of **Relative Risk**.

Cohort study: A study which follows those with an exposure of interest (usually over a period of years), and compares their incidence of disease or mortality with a second group, who are unexposed or exposed at a lower level. Is the incidence rate higher in the exposed workers than the unexposed/less exposed group? Sometimes the cohort is followed forwards in time ('prospective' cohort study), but sometimes the experience of the cohort is reconstructed from historic records ('retrospective' or 'historic' cohort study). The ratio of risk in the exposed relative to the unexposed can be expressed in various ways, such as a **Relative Risk** or **Standardised Mortality Ratio**.

Nested case-control study: A form of **case-control study** in which the cases and controls all come from within a well-defined cohort. Controls are selected from subjects that are at risk at the time that a new case arises - in effect, a **cohort study** in which only some of the non-cases are sampled (for various legitimate reasons – e.g. lowering the costs of special investigations).

Measures of association

Relative Risk (RR): A measure of the strength of association between exposure and disease. RR is the ratio of the risk of disease in one group to that in another. Often the first group is exposed and the second unexposed or less exposed. *A value greater than 1.0 indicates a positive association between exposure and disease*.

(This may be causal, or have other explanations, such as bias, chance or **confounding**.)

Odds Ratio (OR): A measure of the strength of association between exposure and disease. It is the odds of exposure in those with disease relative to the odds of exposure in those without disease, expressed as a ratio. For rare exposures, odds and risks are numerically very similar, so the OR can be thought of as a **Relative Risk**. *A value greater than 1.0 indicates a positive association between exposure and disease*. (This may be causal, or have other explanations, such as bias, chance or **confounding**.)

Standardised incidence ratio (SIR): An SIR is the ratio of the observed number of cases of disease (e.g. cancer) to the expected number of cases, multiplied by 100. The ratio is usually adjusted to take account of differences in the population evaluated with the comparison or "normal population", due to age, gender, calendar year, and sometimes geographical region or socioeconomic status.

Standardised hospitalization ratio (SHR): Similar to the SIR, the SHR is a measure of the strength of association between exposure and hospital admission from a given cause. The SHR is the ratio of the number of new hospital admissions (due to a given disease arising from exposure to a specific risk factor) that occurs within the study population to the number of admissions that would be expected if the study population had the same rate of admission as the general population (the standard).

By convention, SIR and SHRs are usually multiplied by 100. Thus, an SIR (or SHR) of 200 corresponds to a RR of 2.0. For ease of understanding in this report, SIRs and SHRs are quoted as if RRs, and are <u>not</u> multiplied by 100. Thus, *a value greater*

than 1.0 indicates a positive association between exposure and disease. (This may be causal, or have other explanations, such as bias, chance or **confounding**.)

Other epidemiological terms

Confidence Interval (CI): The **Relative Risk** reported in a study is only an *estimate* of the true value in the underlying population; a different sample may give a somewhat different estimate. The CI defines a plausible range in which the true population value lies, given the extent of statistical uncertainty in the data. The commonly chosen 95%CIs give a range in which there is a 95% chance that the true value will be found (in the absence of bias and confounding). *Small studies generate much uncertainty and a wide range, whereas very large studies provide a narrower band of compatible values*.

Confounding: Arises when the association between exposure and disease is explained in whole or part by a third factor (confounder), itself a cause of the disease that occurs to a different extent in the groups being compared.

For example, smoking is a cause of lung cancer and tends to be more common in blue-collar jobs. An apparent association between work in the job and lung cancer could arise because of differences in smoking habit, rather than a noxious work agent. Studies often try to mitigate the effects of ('control for') confounding in various ways such as: restriction (e.g. only studying smokers); matching (analyzing groups with similar smoking habits); stratification (considering the findings separately for smokers and non-smokers); and mathematical modelling (statistical adjustment).

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